Remarks

Election/Restrictions

The pending claims are the subject of a restriction requirement. Only claims with SEQ ID NO: 41 were examined and are now pending. Please see the amendments in the claim listing above, which now lists the pending examined claims. New claims 62 - 71 are added as dependent claims. The new claims find support in the application on page 21, line 29; page 43, line 23; page 45, line 23 and page 45, line 24-26.

Status of claims

Claims 41 - 60 and 62 - 71, relating to SEQ ID NO: 41 are pending.

Information Disclosure Statement

Applicant thanks the Examiner for receiving and accepting the filed IDS submitted on 11 November 2006, 19 October 2006, 25 April 2005 and 22 July 2004. Applicant submitted an additional supplemental information disclosure (IDS) statement on 25 October 2007. Applicant is filing the necessary fee for filing such IDS and would appreciate its contents as being considered as part of this application.

Claim Objections

The claims were rejected because they recited non-elected sequences. This objection is now moot as the pending claims refer to the elected and restricted sequence, SEQ ID NO: 41.

Priority

Verification of the claim of priority to 16 October 1998 is noted.

Claim rejections – Obviousness type double patenting.

Applicant traverses the obviousness type double patenting rejection. The claims are rejected under the obviousness type double patenting rejection because of the allowance of the parent case which issued into US 6,962,978. Applicant's traverse is based on two grounds, first the rejection is not ripe because the pending claims have not been allowed. Only when it is determined that the pending claims are allowable is the rejection proper. The second ground of traversal is that the claims in US 6,962,978 are directed to a composition having a different peptide sequence and that was previously made the subject of a restriction requirement. That subject matter was considered and treated by the USPTO as patentably distinct subject matter. Labeled and treated as such

by the Patent Office, it should not now be subjected to an obviousness type double patenting rejection.

Claim rejections – 35 USC § 112

Claims 41, 43, 58, 59, 60,62 were rejected under 35 USC § 112 because the claims included the phrase " ... any one of SEQ. ID. NO. ..." This phrase has been removed from the pending claims and these objections are moot.

Claim rejections – 35 USC § 103, Item 7a.

In item 7a of the Office Action, claims 41-42, 45-46, 49-50, 53-59 and 62 were rejected under 35 USC 103(a) as unpatentable over Mark *et al.* (WO 8302461), in view of Katre et al. (US 4,766,106). The Examiner stated Mark *et al.* taught the sequence of isolated interferon-beta-1a having the same sequence as the claimed SEQ ID NO: 41. In the Office Action it was argued that Katre *et al.* disclosed "a biologically active interferon-beta" although with a serine substitution at position 17, conjugated to a polyethylene glycol polymer, concluding, "therefore it would have been *prima facie* obvious to combine the teaching of Mark *et al.* with Katre *et al.* to produce a conjugated IFN-beta similar to applicant's invention." The Examiner noted that Katre *et al.* taught that modifying the IFN-beta by pegylating it renders it more soluble, while retaining the desired activity and also increases the *in vivo* half life. The Examiner concluded, "One of ordinary skill in the art would have been motivated to combine the teaching of Mark *et al.* and Katre *et al.,* because it was known at the time of filing that IFN-beta was useful as an antiviral drug and improving its solubility and increasing its in vivo half-live would have been a highly advantageous endeavor."

Applicant agrees that Mark *et al.* discloses the same peptide sequence as SEQ ID NO: 41 in the pending claims. However, applicant's interferon is more than just the peptide sequence disclosed in SEQ ID NO: 41, and by Mark *et al.* The Mark *et al.* compound and applicant's compounds are two very different molecules.

The different compounds are made differently, they have different components, different structures and different properties. Mark *et al.* does disclose interferon-beta-1a, however, it is produced in *E. coli* bacteria and thus it is not glycosylated. See Mark *et al.*, Example 1, page 13, line 28, "When grown in shake-flasks, the *E .coli* strain carrying pDM101/trp/β expresses ..." Applicant's invention starts with interferon-beta-1a, which is produced in mammalian cells and is glycosylated. It is not produced by *E. coli* bacteria.

The Katre *et al* reference also describes a very different type of compound than what applicant claims, in part because Katre *et al* uses interferon-beta-1b and applicant uses interferon-beta-1a.

> "These studies indicate that, despite the conservation in sequence between interferon-beta-1a and interferon-beta-1b,

> they are distinct biochemical entities and therefore much of what is known about interferon-beta-1b cannot be applied to interferon-beta-1a and vice versa."

Applicant's specification, page 2, line 23-26, emphasis added.

The Katre *et al* reference also describes a very different type of pegylation. This is described in more detail below.

Case law requires one to consider an entire compound with all of its characteristics when considering the obviousness of chemical structures. *In re Pleuddemann,* 910 F.2d 823, 15 USPQ2d 1738 (Fed. Cir. 1990). "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." *Id.*

> "But a formula is not a compound and while it may serve in a claim to identify what is being patented, as the metes and bounds of a deed identify a plot of land, the thing that is patented is not the formula but the compound identified by it. And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous. *In re Papesch,* 137 USPQ 43, 315 F.2d 381 at 391 (CCPA 1963). (emphasis added)

Just as a compound should be considered for all of its properties, so too should a reference be read for all that it teaches, rather than for bits and pieces lifted with the benefit of hindsight. Katre *et al.* teaches that it is possible to attach numerous PEG molecules to various places, preferably on lysine residues, on a non-glycosylated form of interferon-beta known as the "1b" form. The examiner takes Katre *et al.*'s teaching about pegylation of interferon-beta-1b, and then combines it with the Mark *et al.* reference, which does not teach anything about pegylation.

If one skilled in the art were to do what the Examiner suggests, combine Katre *et al.* with Mark *et al.,* one skilled in the art would in fact not be able to predict the resulting properties of the interferon. Applicant knows this because they have essentially independently performed some of the same experiments described in the references. The results were indeed surprising and unpredicted. Attached to this response is a Declaration from a scientist who works for the assignee but is not an inventor. In that Declaration is data that shows if one were to start with interferon-beta-1a and attach PEG in a manner similar to that suggested by Katre *et al.*, that is by using non-specific pegylation chemistries which tend to favor lysine attachments, then one is likely to get an interferon-beta-1a PEG composition with little activity and which is basically useless.

Applicant submits the Darren P. Baker Declaration (the "Declaration") to demonstrate that one cannot simply mix and match a reference that refers to interferon-

beta-1a with a reference that teaches pegylation of non-glycosylated interferon-beta-1b and assume one would have predictable results.

The attached Declaration shows the results of activity tests when one makes a Katre *et al.*, type of non-specific pegylation using 5 and 20 kDa PEG conjugated to interferon-beta-1a. Figure 1 shows antiviral activity. Lines with open circles or diamonds are controls, with the ingredients of the mixtures present but no PEG being present. Note how the 20 kDa PEG sample drops to the bottom of the chart. The 20 kDa PEG sample shows very little, if any, antiviral activity. Figure 2 shows antiproliferative activity of similar samples. The more active the sample, the lower the [3H] thymidine incorporation. Figure 2 shows the 20 kDa PEG sample is at the top of the figure, showing little antiproliferative activity. This data demonstrates the unpredictable nature of the art and that if anything, the variable and multiple pegylation disclosed by Katre *et al.*, teaches away from applicant's invention.

Mark *et al.* teaches how to make "Multiclass Hybrid Interferons" which combine parts of interferon-alpha with parts of interferon-beta. (Please note with interferon, alpha and beta should not be confused with 1a and 1b) The hybrid interferons were an attempt to reduce some of the side effects of interferon. Mark *et al.* was trying to get away from wild type interferon. Accordingly, he suggests the wild type peptide has undesireable properties.

> "Because of their restricted activity such treatment [cell growth regulating activity] is not expected to be associated with side effects such as immunosuppresson that often is observed with conventional nonhybrid interferon therapy."

See pg. 34 lines 19-23 of Mark *et al.* (WO 83/02461)

Contrast Mark *et al.*'s disclosure to the applicant's invention. Applicant is not trying to reduce interferon-beta side effects, rather applicant makes a new composition with "the salutary properties of pegylated proteins in general with no effective loss in activity as compared to interferon-beta-1a forms that are not conjugated." Page 2-3, lines 31-1. Applicant makes something new, a "polymer-interferon-beta-1a conjugate[s] [that] retain[s] all or most of their biological activities,..." Specification page 3, lines 2-3. In the hope of making something with "increased half-life and alterations in tissue distributions (e.g., ability to stay in the vasculature for longer periods of time), increased stability in solution, reduced immunogenicity, protection from proteolytic digestion and subsequent abolition of activity." Page 3, lines 4-7.

The Mark *et al.* compound was created for a very different reason than applicant's compound, and it is a very different compound compared to applicant's invention. If one simply attempts to pegylate interferon-beta-1a, variously and multiply, then one is likely to end up with a composition of very little activity, as shown in the attached Declaration.

Examiner's reliance on Katre *et al.* to support an obviousness rejection in combination with Mark *et al.* is similarly misplaced. Like Mark *et al.*, the Katre *et al.*

interferon was not glycoslyated. In addition the Katre *et al.* form of interferon-beta-1b, form rather than the interferon-beta-1a, which is claimed here. As the Examiner noted, the Katre *et al.* interferon has a serine 17 substitution.

The glycosylation difference between the interferon-beta-1a versus the beta-1b form is neither academic nor of small importance. The non-glycosylated form of interferon-beta-1b is not soluble. The reason Katre *et al.* performed the conjugation was to make the insoluble, unglycosylated interferon-beta-1b soluble and more like the glycosylated form of interferon. See col. 4, lines 2-6 of Katre *et al.*

> "This modification may be mimicking glycosylation of the protein, thereby surprisingly rendering the protein soluble as the native glycosylated protein is soluble."

The primary goal, the whole purpose, of the Katre *et al.* process, was to make an insoluble protein soluble. One would have no reason to use a similar process on an already soluble protein. "This modification [solubilization] also avoids addition of extraneous solubilizing additives such as detergents or denaturants to keep the protein in solution." Katre *et al.* at col. 4, lines 5-8.

Katre *et al.* does not teach one skilled in the art to expect greater activity from the pegylation. Katre *et al.* teaches that one should not expect to find it results in a protein with greater activity, rather at best, it says, one should expect the activity to drop by half. "Preferably, at least about 50% of the biological activity of the protein is retained, and most preferably 100% is retained." See col. 9, lines 35-37. Not an increase. The entire column, 9, describes the process and expectations for the process. It is true that Example VI starting on col. 18, lines 60 provides one example of a non-glycosylated interferon-beta PEG conjugated protein having greater activity than non-conjugated. In Example VI, there is a description of a reaction containing 0, 10, 20 or 50 moles of PEG per mole of interferon-beta -1b (non-glycosylated). The results, provided in Example VII, Table III, col 19, lines 47-57, show that the activity of the non-conjugated protein, (0 amount) compared to conjugated protein. At 0, 10 and 20 moles of PEG per mole of interferon-beta-1b it shows PEG v. no-PEG are all about the same. Only at the highest concentration of PEG, 50 moles PEG per mole interferon-beta -1b, does it appear that PEG interferon has greater activity than no PEG. Thus, the data from Katre *et al.* indicate 0, 10, and 20 moles PEG are all similar. Given the wide error range of the data and the lack of a dose response, the numbers do not really point in any direction. In addition, the Katre *et al.* data was with a different compound. The attached Declaration shows the Katre interferon-beta-1b PEG is different and behaves very differently than the interferon-beta-1a PEG made by the applicant.

To one skilled in the art, if Katre *et al.* teach anything it is that to achieve greater activity over native protein, when using PEG, one should use very high concentrations of PEG. These are levels far exceeding what applicant describes. Applicant's description teaches 1 to 10 moles of activated polymer per mole of protein. See specification, page 18, line 30. Applicant's invention is in fact **one molecule** of PEG per molecule of peptide. The PEG only attaches at the N-terminus and this limitation is in the pending

claims. Katre *et al.* requires at least 5 times more activated PEG polymer to achieve greater than "no-PEG" activity. Assuming that the Katre *et al.* data point for 50 moles PEG per mole interferon-beta-1b is reproducible, one would have no expectation of creating what the applicant did and having a useful interferon-beta-1a, by following the methods of Katre *et al.*

Katre *et al.* started with an insoluble protein, taught 5 times higher level of activated PEG per mole of protein, and failed to explain how one could selectively activate the N-terminal or C-terminal of the protein.

Katre *et al.* actually prefers to *avoid* putting PEG on the N-terminus.

> "While the residues may be any reactive amino acids on the protein, such as one or two cysteines or the N-terminal amino acid group, preferably the reactive amino acid is lysine, which is linked to the reactive group of the activated polymer through its free epsilon-amino group, or glutamic or aspartic acid, which is linked to the polymer through an amide bond."

Katre *et al.* at col. 8, lines 28-35.

Kate *et al.* does make a passing reference to an N-terminal conjugation – but only for a non-glycosylated protein. Even there it is simply one of many untried possibilities and it is not advised. If increased activity is sought, Katre *et al.* recommends bonding the PEG with lysines, not the N-terminus. Katre *et al.* explains it is more preferable to conjugate up to ten amino acids.

> "In one preferred embodiment the protein is covalently bonded via one or two of the amino acid residues of the protein, preferably lysines, for maximum biological activity. In another preferred embodiment, the protein is covalently bonded via up to ten of the amino acid residues of the protein, preferably lysines, with higher substitutions generally increasing the circulatory life of the protein." See Katre *et al.* col 8, lines 36-43.

Katre *et al.* suggest conjugating the lysine residues because there are a lot of them and that is how one gets increased activity, at least according to Katre *et al.* This is in stark contrast and opposite to the teaching of applicant where relatively low concentrations of PEG per mole of protein are used.

Katre *et al.* doesn't teach N-terminal conjugated proteins of any type, certainly not a glycosylated interferon-beta-1a. Katre *et al.* only teaches 0, 10, 20 and 50 moles of activated polymer per mole of protein. Even at the lowest level described, 10 moles of activated polymer per mole of protein, there is little chance of a selective N-terminal conjugation using the Katre *et al.* procedures.

Under the Katre *et al.* conditions, lysine conjugation is preferred. Katre *et al.* does not mention or refer to even one document that would teach how to make an N-terminal conjugation. The fair conclusion is that Katre *et al.* teaches away from N-terminal interferon-beta-1a PEG conjugation, not toward it.

One skilled in the art reviewing Katre *et al.* and thinking about pegylation of interferon would also be confronted with huge number of alternative possibilities when considering PEG interferon conjugation. For example, the interferon proteins of Katre *et al.* might be conjugated by attaching a PEG moiety in any of the following ways:

1) to any amino acid or point of conjugation, including but not limited to the following,
2) to the C-terminus site
3) to any lysine residues, including the epsilon - lysine residues (Katre most preferred)
4) to any or a specific free carboxylic group
5) to any or a specific activated carbonyl group
6) to any or a specific hydroxyl group
7) to any or a specific guanidyl group
8) to any or a specific oxidized carbohydrate group
9) to the alpha amino at the N-terminal
10) to any cysteine residues or to any mercapto groups
11) to glutamic or aspartic acid residues
12) to any number of combinations of the groups in 1-12 noted above.

See p. 18, lines 15-21 of applicant's specification and other sources.

In Katre *et al.*, conjugation to lysine residues is always either preferred or most preferred. The only example taught by Katre *et al.* favored general lysine conjugation (Example VII). The only example achieving greater activity for the conjugated protein than over unconjugated was with 50 moles of activated polymer per mole of protein. There is no dose response effect seen with the Katre *et al.* data, which tells one skilled in the art that it was either an erroneous data point or that unpredictable factors were affecting the results.

Finally, neither Katre *et al.* nor Mark *et al.* discuss what complications could arise when attempting to conjugate PEG with a glycosylated interferon-beta instead of a non-glycosylated protein. Mark *et al.* doesn't mention PEG conjugation. Katre *et al.* doesn't discuss PEG conjugation to a glycosylated interferon-beta because glycosylated interferon-beta is already soluble.

Contrast the processes described by Katre *et al.* and Mark *et al.* to the applicant's description of their invention.

> "We used a reaction scheme in which this selectivity is maintained by performing reactions at low pH (generally 5-6) under conditions where a PEG-aldehyde polymer is reacted with interferon-beta-1a in the presence of sodium cyanoborohydride. This results, ...in an interferon-beta-1a

whose N-terminus is specifically targeted by the PEG moiety.
Page 19, lines 25-30.

There is nothing in Katre *et al.* or Mark *et al.* to suggest this type of selective targeting or how to achieve it. It was only because of applicant's investigation and experimentation that an N or C terminal PEG conjugation was ever considered.

"We found unique sites(s) for polymer attachment that would not destroy function of the interferon-beta-1a. In addition, we also used site-directed mutagenesis methods to independently investigate sites(s) for polymer attachment (See Example 1)."
Specification p. 16, line 19-21.

"These mutational analyses demonstrated that N- and C- termini lie in a portion of the interferon-beta molecule not important for receptor binding or biological function."
Specification p. 17, lines 7-8.

"We used a reaction scheme in which this selectivity is maintained by performing reactions at low pH (generally 5-6) under conditions where a PEG-aldehyde polymer is reacted with interferon-beta-1a in the presence of sodium cyanoborohydride. This results, ...in an interferon-beta-1a whose N-terminus is specifically targeted by the PEG moiety."
Specification p. 19, lines 25-30.

Applicant teaches how to attach to both the N and C terminus. "N-terminus is preferred." Page 18, line 23. "Secondary sites are at or near the C-terminus" p. 18, line 24. Once made the advantages became apparent.

"They have long circulation in the blood yet are easily excreted from living organisms. They may be prepared by dissolving in water or acceptable liquid medium. They can be formulated in liquid or dry powder formulations."
Specification p. 23. See also p. 24 of the specification.

The Examiner argues that since the advantages of PEG conjugation are known to provide longer circulation half life when applied to other forms of interferon it would be obvious to pegylate the glycosylated interferon-beta-1a. Applicant has explained first, interferon-beta-1a is already soluble so one would not ordinarily think of doing it, second if one does make a non-specific peglyation of interferon-beta-1a, the result is likely to be an interferon with little or no activity. Applicant started with interferon-beta-1a, already 10 times more active than interferon-beta-1b, (see specification p. 2, line 13) and already soluble, and then made an N-terminal pegylation of the glycosylated peptide. There is no obvious need to make the beta-1a form more active. Should one press ahead and use the Katre *et al.* methods anyway, on interferon-beta-1a, the result is likely to be a protein with diminished activity if not an inactive one.

Applicant respectfully requests the obviousness rejection be withdrawn.

Claim rejections – 35 USC § 103, Item 7b.

In item 7b of the Office Action, claims 43, 44, 47, 48, 51 and 52 were rejected under 35 USC § 103(a) as unpatentable over Mark *et al.* (WO 8302461), in view of Katre *et al.* (US 4,766,106) in further view of Capon *et al.* (US 5,116,964). The Examiner referred to the previous arguments of item 7a, discussed above, and then added that Capon *et al.* teach chimeric polypeptides comprising ligand binding partners fused to stable plasma proteins which are capable of extending the *in vivo* plasma half-life of the ligand binding partner. In particular Capon *et al.* states the immunoglobulin (Ig) fusions of the invention "serve to prolong the *in-vivo* plasma half-life of the ligand binding partner..." and "facilitate its purification by protein A." See the Office Action citations to Capon *et al.*, page and line omitted.

Applicant responds to the Examiner's rejections first by noting that all the rejected claims under item 7b are dependent on, and have all the elements of, the claims rejected under item 7a. If applicant's arguments above are accepted, then the dependent claims in item 7b should also be allowed.

Applicant also notes that Capon *et al.* does not appear to mention anything about interferon, whether alpha, beta, 1a, 1b or otherwise. The only examples in Capon *et al.* comprise some form of LHR or Lymphocyte cell surface glycoprotein, murine or human. There are no other examples. LHR acts to mediate the binding of lymphocytes to the endothelium of lymphoid tissue. There is no direct suggestion in Capon *et al.* to use interferon.

In Capon *et al.* the definition of a ligand binding partner includes hundreds of classes of compounds with thousands of different compounds suggested, yet only one is exemplified, LHR. Ligand binding partners in Capon *et al.* include receptors and carrier proteins, hormones, cellular adhesive proteins, tissue-specific adhesion factors, lectin binding molecules, growth factors, enzymes, nutrient substances and the like. Col 2, lines 15-20. If the various types of compounds were to be fully exemplified the list would include thousands if not millions of compounds. The statement mentioned by the Examiner, referring to extended *in vivo* plasma half life from chimeric immunoglobulin (Ig) fusions may be generally true. Applicant is not claiming a general comment like that used in the Examiner's argument.

Applicant's immunoglobulin claims, like claim 48, are specific, and would read as follows if independent. 'A composition comprising a glycosylated interferon-beta-la comprising the amino acid sequence in SEQ ID NO: 41, coupled to a non-naturally-occurring polymer at an N-terminal end of said glycosylated interferon-beta-1a, said polymer comprising a polyalkylene glycol moiety, wherein the interferon-beta-1a is an interferon-beta-la fusion protein, wherein the interferon-beta fusion protein comprises a portion of an immunoglobulin molecule.'

Capon *et al.* refers to a single immunoglobin fusion protein with LRF and it has no apparent application to any type of interferon. As discussed above, applicant's molecules are novel and non-obvious. The Capon *et al.* reference does not make them any less novel or more non-obvious simply because they could also be fused to immunoglobin.

Moreover Capon *et al.* fails to describe in any way attaching an immunoglobin to a pegylated protein.

Applicant respectfully requests the entry of the amendments, consideration of applicant's comments, and the speedy allowance of the pending claims.

Respectfully submitted,

Date: November 21, 2007

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